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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133			CHEN, SHIN LIN	
		ART UNIT	PAPER NUMBER	
		1632		

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/035,596</b>	Applicant(s) <b>Gunzburg et al.</b>
	Examiner <b>Shin-Lin Chen</b>	Art Unit <b>1632</b>
<b>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</b>		
<b>Period for Reply</b> A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.		
<ul style="list-style-type: none"> <li>- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.</li> <li>- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.</li> <li>- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.</li> <li>- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).</li> <li>- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</li> </ul>		
<b>Status</b>		
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Sep 10, 2002</u>		
2a) <input type="checkbox"/> This action is FINAL.      2b) <input checked="" type="checkbox"/> This action is non-final.		
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11; 453 O.G. 213.		
<b>Disposition of Claims</b>		
4) <input checked="" type="checkbox"/> Claim(s) <u>1, 2, 9-14, 16-19, 23-28, 31-33, 36-45, and 47-94</u> is/are pending in the application.		
4a) Of the above, claim(s) _____ is/are withdrawn from consideration.		
5) <input type="checkbox"/> Claim(s) _____ is/are allowed.		
6) <input checked="" type="checkbox"/> Claim(s) <u>1, 2, 9-14, 16-19, 23-28, 31-33, 36-45, and 47-94</u> is/are rejected.		
7) <input type="checkbox"/> Claim(s) _____ is/are objected to.		
8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.		
<b>Application Papers</b>		
9) <input type="checkbox"/> The specification is objected to by the Examiner.		
10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).		
11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.		
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.		
<b>Priority under 35 U.S.C. §§ 119 and 120</b>		
13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of: 1. <input type="checkbox"/> Certified copies of the priority documents have been received. 2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____. 3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). *See the attached detailed Office action for a list of the certified copies not received.		
14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e). a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.		
15) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.		
<b>Attachment(s)</b>		
1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)		
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____		
4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____		
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)		
6) <input type="checkbox"/> Other: _____		

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### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-10-02 has been entered.

Applicants' amendment filed 9-10-02 has been entered. Claims 1, 13, 23, 26, 37-40, 70-74, 79, 91, 92 and 94 have been amended. Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36-45 and 47-94 are pending and under consideration.

#### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 38, 44, 55, 59, 74-81, 91 and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "A retroviral vector comprising a heterologous gene...MMTV U3 sequence homologous to a PCR amplification product...and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template" in claims 1, 13, 23, 26, 74, 79, 91 and 92 is vague and

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renders the claims indefinite. A provirus is a virus that contains its viral genomic DNA in said virus. It is unclear how a retroviral vector can **comprises** a MMTV provirus or how a plasmid can **comprise** a MMTV provirus. It is also unclear what is intended to be claimed: a retroviral vector, a MMTV provirus or a plasmid. Further, the phrase “U3 sequence homologous to a PCR amplification product” in those claims is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered “U3 sequence homologous to a PCR amplification product”. Claims 2, 9-12, 14, 16-19, 24, 25, 27, 28, 31-33, 36, 38, 75-78, 80 and 81 depend on the claims set forth above but fail to clarify the indefiniteness.

The term “proximal 445 bp of the murine WAP promoter” in claims 44 and 55 is vague and renders the claims indefinite. Murine WAP promoter encompasses promoter sequences derived from various murine species. It is unclear what proximal 445 bp of which WAP promoter is intended. It is unclear as to the metes and bounds of “proximal 445 bp of the murine WAP promoter”.

Applicants argue that Kolb teaches the proximal regions of the WAP promotor (amendment, p. 7). This is not found persuasive because of the reasons set forth above.

The phrase “select from the group consisting of: Herpes Simplex Virus thymidine kinase gene...**or** cytokines genes” in claim 11 is vague and renders the claim indefinite. It is unclear what genes are included in the group. Changing the term “or” to “and” would be remedial.

The phrase “select from the group Herpes Simplex Virus thymidine kinase gene...**or** cytokines genes” in claims 32 and 59 is vague and renders the claim indefinite. It is unclear what

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group is intended. Herpes Simplex Virus thymidine kinase gene is not a group. Changing the phrase “selected from the group... or” to “selected from the group consisting of: ...and” would be remedial.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36-45 and 47-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for construction of vectors pMMTV-BAG and pWAP-BAG containing  $\beta$ -galactosidase gene under the control of MMTV and WAP, respectively, and the expression of  $\beta$ -galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above, does not reasonably provide enablement for any retroviral vector comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter and said therapeutic gene is expressed in a cell *in vivo*, a method of expressing said therapeutic gene in a human cell *in vivo*, any pharmaceutical composition comprising a DNA construct, a retrovirus particle, or a cell line, expressing any therapeutic gene under the control of a MMTV promoter or a WAP promoter, and a method for the treatment of human mammary carcinoma comprising administering to a human said pharmaceutical composition expressing any therapeutic gene under the control of a MMTV

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or WAP promoter *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a retroviral vector comprising a therapeutic gene under the control of a MMTV promoter or a WAP promoter and said therapeutic gene is expressed in a cell, such as a human cell, a method of expressing said therapeutic gene in a human cell, a pharmaceutical composition comprising a DNA construct, a retrovirus particle, or a cell line, expressing said therapeutic gene under the control of a MMTV promoter or a WAP promoter, and a method for the treatment of human mammary carcinoma comprising administering to a human said pharmaceutical composition expressing said therapeutic gene under the control of a MMTV or WAP promoter.

The claims are also drawn to a retroviral vector comprising a heterologous gene under the control of a MMTV promoter or a WAP promoter and said heterologous gene is expressed in a cell, such as a human cell, a method of expressing said heterologous gene in a human cell, a recombinant retroviral particle or provirus comprising said retroviral vector or a DNA construct containing a heterologous gene under the control of a MMTV promoter or WAP promoter, a packaging cell line harboring said retroviral vector, and isolated human cell comprising said retroviral vector, and a capsule encapsulating said packaging cell line.

The claims read on expression of a therapeutic gene *in vitro or in vivo*. The claims also read on the use of the retroviral vector, the retroviral particle or provirus containing said

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retroviral vector or the DNA construct set forth above, the packaging cell line comprising said retroviral vector, the human cell containing said retroviral vector and encapsulated cells containing said packaging cell line for gene therapy *in vivo* in light of the specification.

The specification of the instant invention discloses the construction of vectors pMMTV-BAG and pWAP-BAG containing  $\beta$ -galactosidase gene under the control of MMTV and WAP, respectively. The specification shows the expression of  $\beta$ -galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above.

A pharmaceutical composition is a composition which implies *in vivo* applicability such that therapeutic effects against a particular disease or a disorder are obtained. It was well known in the art that  $\beta$ -galactosidase is a molecular marker and not a therapeutic gene, and such is generally not considered to be indicative of therapeutic gene expression. The expression of a  $\beta$ -galactosidase in explanted normal primary human mammary tissue infected with vectors pMMTV-BAG and pWAP-BAG is not considered to enable therapeutic gene expression under the control of a MMTV promoter or a WAP promoter, since expression of a marker gene does not correlate with expression of a gene *in vivo*, such that the expression provides therapeutic effect for a therapy. The specification fails to provide evidence that expression of a marker gene relates in any way to successful expression of other genes for providing therapeutic effect for gene therapy *in vivo*.

The specification fails to provide adequate guidance and evidence that administration of a vector expressing a  $\beta$ -gal or any therapeutic gene product *in vitro* or *in vivo* would provide

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sufficient expression of said β-gal or said therapeutic gene product for a duration of sufficient time to effect therapeutic effects for a particular disease or disorder, such as disorders or diseases of human mammary cells *in vitro* or *in vivo*. The specification fails to provide adequate guidance and evidence for the sufficient expression of any heterologous gene or any therapeutic gene under the control of any MMTV promoter or any WAP promoter in the retroviral vector or other vector for sufficient time *in vivo* such that therapeutic effects are provided for a particular disease or disorder, or for using said retroviral vector expressing any heterologous gene or therapeutic gene for the treatment of disorders or diseases of human mammary cells *in vitro* or *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and is highly unpredictable. Verma et al., 1997 (Nature, Vol. 389, pages 239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (see Verma et al., page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the

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cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e.g., bridging pages 81-82). Verma states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that “the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression” for gene therapy, and obstacles to gene therapy *in vivo* include “the development of effective clinical products” and “the low levels and stability of expression and immune responses to vectors and/or gene products” (e.g. abstract). The instant specification does not provide any *in vitro* or *in vivo* working examples for gene therapy. The specification only shows the expression of β-galactosidase in explanted normal primary human mammary tissue infected with retrovirus containing the vectors set forth above but fails to teach one skilled in the art how to deliver the retroviral vector, retroviral particle, packaging cells, or capsule to a subject via various administration routes such that it reaches targeted cells and provide sufficient expression of gene product so as to effect a therapeutic response to any particular disease or disorder *in vivo*.

Shao et al., 1994 (Polym. Prepr. Vol. 35, No. 2, p. 59-60) shows that encapsulated cells may be used for prolong delivery of a granulocyte-macrophage colony stimulating factor (GM-CSF) to a tumor site. However, Aebischer et al., 1991 (Journal of Biomech. Eng. 113(2), p. 178-

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183) reports various problems of encapsulated cells for the treatment of disorder or diseases.

Aebischer encapsulated PC12 cells in polyelectrolyte-based microcapsules or thermoplastic-based macrocapsules and maintain *in vitro* or transplanted in a rat experimental Parkinson model for 4 weeks. They point out that unencapsulated PC12 cells can lead to the formation of lethal tumors in rats, and do not survive if transplanted into the nervous system of either guinea pigs or mice. The presence of a hydrogel within the microcapsule core possibly impeded cell movement within the capsule, resulting in densely-packed cell aggregates and because their poor mechanical properties, microcapsules are more difficult to implant. Often the implanted microcapsules lost their spherical shape and the retrieval of microcapsules is not possible without significant injury to the brain. In addition, alginic-like materials is found in the vicinity of some microcapsules rasing questions about the stability of the microcapsules *in vivo*. It is also unclear whether the encapsulated cells will grow within the microcapsule, although the encapsulated cells does not trigger immune response from the host as shown by Aebischer. When the cells do grow and continue to grow within the microcapsule, the cells could burst out of microcapsule and trigger immune response. The claimed invention encompasses any type of cells containing therapeutic gene under the control of a WAP promoter for the treatment of disease of human mammary cells, administration of cells into immunologically incompatible host, between different species or different individuals in same species for example, would stimulate immune response from the host. Therefore, it would be unpredictable whether cells or encapsulated cells containing any

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therapeutic gene would exhibit any therapeutic effect on treating disease of human mammary cells *in vivo*. The specification as filed fails to provide any particular guidance for such.

In view of the lack of guidance in the specification on how to treat a particular disease or disorder or disorders or diseases of human mammary cells with encapsulated cells containing a construct comprising a heterologous gene or a therapeutic gene under the control of a MMTV promoter or a WAP promoter and the unpredictability of gene therapy *in vivo*, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

The specification also fails to provide adequate guidance and evidence for whether any WAP promoter derived from any organism other than mouse can direct gene expression in human mammary cells or any other human cells, and whether a MMTV promoter can direct gene expression in any human cell type other than human mammary gland cells. The specification indicates that “One regulatory element demonstrated to give rise to expression in the pregnant and lactating mouse mammary gland is a small region of the rodent WAP promoter. It is therefore not predictable that this regulatory element will function at all to direct expression in human mammary cells and/or allow expression in human mammary carcinoma cells” (specification, page 2, lines 15-25). The mechanisms of stimulating downstream gene expression

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of various WAP promoters derived from different organisms may vary because the difference of the core elements of WAP promoters and the cellular interacting transcriptional factors in the cells may vary from species to species. Therefore, it would be unpredictable whether any WAP promoter other than the mouse WAP promoter will direct gene expression in human mammary cells or any other human cells.

Different cell types may have different mechanisms in the transcriptional control of gene expression and the transcriptional machinery in different cell type could differ. Thus, gene expression via a MMTV promoter in normal human mammary gland cells or human bladder carcinoma cells does not necessarily imply that the MMTV promoter can direct gene expression in other human cell types. Further, the MMTV promoter is known in the art to be a mammary cell-specific promoter, it is likely that the MMTV promoter can not direct gene expression in any human cell type other than mammary cells.

In view of the lack of guidance and evidence on whether any WAP promoter other than mouse mammary WAP promoter could direct gene expression in human mammary cells or in human mammary carcinoma cells, on whether a MMTV promoter can direct gene expression in any human cell type other than human mammary gland cells or human bladder carcinoma cells, and the unpredictable nature of a WAP promoter or a MMTV promoter in directing gene expression in different cell types for gene therapy *in vivo*, it would have required a skilled person in the art at the time of the invention undue experimentation to have practiced over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of

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the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that the specification teaches the preparation of the claimed retroviral vector, retroviral particles, how to infect mammary cells, methods for assessing the activity of WAP or MMTV promoter, preparation of retroviral vector expressing cytochrome P450 under the control of WAP promoter, how to encapsulate a packaging cell and implant the capsule in mammary tissue (amendment, p. 8-9). This is not found persuasive because of the reasons set forth above. The specification fails to provide sufficient enabling disclosure for the full scope of the claimed invention. As discussed above, the art of gene therapy *in vivo* was unpredictable at the time of the invention. One major obstacle to successful gene therapy *in vivo* has been the inability to deliver genes efficiently and obtain sustained expression. The fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. In addition, delivery route also plays an important role in efficient gene transfer and sufficient gene expression for gene therapy. The claims encompass

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any therapeutic gene, including unidentified gene, for gene therapy *in vivo*. The specification fails to provide correlation between a therapeutic gene and a particular disease or disorder for gene therapy *in vivo*. The specification also fails to provide adequate guidance and evidence for the sufficient expression of any heterologous gene or any therapeutic gene under the control of any MMTV promoter or any WAP promoter in a retroviral vector, a retrovirus particle, cells or encapsulated cells for sufficient duration of time *in vivo* such that therapeutic effects are provided for a particular disease or disorder, or for using said retroviral vector expressing any heterologous gene or therapeutic gene for the treatment of disorders or diseases of human mammary cells *in vivo*.

Applicants argue that the technique for preparing the retroviral vector and the retroviral vector function were known in the art, and the use of retroviral vector in treating disease is well accepted in the art. Applicants cite references (Exhibits 1-3) that teaches different example of gene therapy using retroviral vector, and no undue experimentation is required (amendment, p. 9-10). This is not found persuasive because of the reasons set forth above. Since gene therapy *in vivo* was unpredictable at the time of the invention, each gene therapy case has to be considered case by case. Result of one gene therapy *in vivo* can not be extrapolated to the success of other gene therapies *in vivo*.

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5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 53, 54, 58-61, 67-69, 82, 83 and 85-88 are rejected under 35 U.S.C. 102(e) as being anticipated by Barber et al., 2001 (Us patent No. 6,241,982).

The claims are directed to a retroviral vector comprising a heterologous gene or a therapeutic gene, such as a cytokine gene, under the control of a WAP regulatory sequence, wherein the WAP regulatory sequence drives gene expression in a cell, such as a human cell, a recombinant retroviral particle or provirus comprising said retroviral vector, a packaging cell line harboring said retroviral vector, and a pharmaceutical composition comprising said retroviral vector, retroviral particle or retroviral provirus.

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Barber teaches preparation of a recombinant retroviral vector or retrovirus expressing a cytotoxic gene, such as a cytosine deaminase gene, under the control of WAP promoter, production of vector particle by using producer cells, and a pharmaceutical composition comprising said retroviral vector, and retroviral particles and a pharmaceutical acceptable carrier or diluent (e.g. abstract, column 4, 5, 20, 35, 36). Thus, claims 53, 54, 58-61, 67-69, 82, 83, 85-88 are anticipated by Barber.

It should be noted that claims 53, 54, 58-61, 67-69, 82, 83 and 85-88 are product claims. The elements encompassed in the claimed retroviral vector are a heterologous gene or therapeutic gene and the WAP regulatory sequence. The intended use of the WAP regulatory sequence in driving gene expression in human cells is irrelevant for 102 rejection. Further, the term "pharmaceutical" does not carry weight in 102 rejection.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 53, 54, 58-61, 67-69, 82, 83, 85-88 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dranoff et al., 1993 (PNAS, USA, Vol. 90, p. 3539-3543) in view of

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Mehigh et al., 1993 (Journal of Animal Science, Vol. 71, p. 687-693) and Shao et al., 1994 (Polym. Prepr. Vol. 35, No. 2, p. 59-60).

The claims are directed to a retroviral vector comprising a heterologous gene or a therapeutic gene, such as a cytokine gene, under the control of a WAP regulatory sequence, wherein the WAP regulatory sequence drives gene expression in a cell, such as a human cell, a recombinant retroviral particle or provirus comprising said retroviral vector, a packaging cell line harboring said retroviral vector, a capsule comprising said cells, and a pharmaceutical composition comprising said retroviral vector, retroviral particle or retroviral provirus.

Dranoff teach subcloning DNA sequences encoding the cytokine such as IL-4, IL-6,  $\gamma$ -IFN, a granulocyte-macrophage colony stimulating factor (GM-CSF), and adhesion molecules into retroviral vector MFG which contains Moloney murine leukemia virus (Mo-MuLV) long terminal repeat (LTR) and the resulting construct are introduced into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells. The transduced B16 cells are inoculated subcutaneously into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene (see e.g. abstract; result, first and second columns).

Dranoff does not teach using WAP promoter for the expression of a gene in a retroviral vector, and a capsule encapsulating the packaging cell line and said capsule comprising a porous capsule wall surrounding said packaging cell line.

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Mehigh teaches development of a recombinant bovine leukemia virus (BLV) vector for delivery of a synthetic bovine growth hormone-relating factor (bGRF) gene into bovine cell, wherein the bGRF gene is under the control of WAP promoter or MMTV promoter. Mehight also teaches preparation of virus particles and the use of said viral particles to deliver the bGRF gene by viral infection into fresh MDBK cells (e.g. abstract).

Shao teaches microcapsules composed of collagen and encapsulated B16-F10 cells transduced with retrovirus containing GM-CSF gene into said microcapsule, and monitor the secretion of GM-CSF in the culture medium (e.g. experimental).

It would have been obvious for one of ordinary skill in the art at the time the invention to substitute the Mo-MuLV LTR as taught by Dranoff with WAP promoter as taught by Mehight for the construction of a recombinant retroviral vector containing any desired gene, a recombinant retrovirus containing said retroviral vector, or packaging cells harboring said retroviral vector, and a capsule encapsulating said packaging cells for the expression of any desired gene product in a cell, because Mo-MuLV LTR and WAP promoter both are regulatory sequences derived from LTR and they both have function of directing gene expression, and Dranoff and Mehight teach construction of viral vector expressing a desired gene under the control of either WAP promoter or Mo-MuLV LTR. Th buffer solutions containing the retroviral vectors, the retroviral particles, or the cells are considered pharmaceutically acceptable carrier or diluent.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to produce a retroviral vector comprising a heterologous gene or a

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therapeutic gene under the control of a WAP regulatory sequence, a recombinant retroviral particle produced by culturing a packaging cell line harboring said retroviral vector, a retroviral provirus carrying a construct comprising a heterologous gene or a therapeutic gene under the control of a WAP regulatory sequence as taught by Dranoff and Mehigh, and a capsule encapsulating the packaging cells for monitoring the secretion of gene product in cell culture medium as taught by Shao with reasonable expectation of success.

It should be noted that claims 53, 54, 58-61, 67-69, 82, 83, 85-88 and 90 are product claims. The elements encompassed in the claimed retroviral vector are a heterologous gene or therapeutic gene and the WAP regulatory sequence. The intended use of the WAP regulatory sequence in driving gene expression in human cells is irrelevant for 103(a) rejection. Further, the term "pharmaceutical" does not carry weight in 103(a) rejection.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

A handwritten signature in black ink, appearing to read "SL Chen".